# Sustained efficacy of natalizumab in the treatment of relapsing-remitting multiple sclerosis independent of disease activity and disability at baseline: real-life data from a Swiss cohort

Kallweit, U ; Jelcic, I ; Braun, N ; Fischer, H ; Zörner, B ; Schreiner, B ; Sokolov, A A ; Martin, R ; Weller, M ; Linnebank, M

Abstract: OBJECTIVES: Therapy for relapsing-remitting multiple sclerosis with natalizumab (Tysabri; Biogen Idec) has been shown to be effective in the reduction of the clinical relapse rate and disability progression. However, real-life longitudinal data, including years before baseline, are rare. METHODS: An observational single-center study was carried out. We analyzed data from 64 consecutive patients with multiple sclerosis. RESULTS: After 1 year of treatment (n = 64), score on the Expanded Disability Status Scale (EDSS) decreased by 0.47 points (P = 0.047) and the annualized relapse rate (ARR) decreased by 82% (P < 0.001). After 2 years (n = 41), EDSS score was still reduced by 0.28 (not significant) and ARR was reduced by 69% (P < 0.001). After 3 years (n = 23), EDSS score was reduced by 0.26 (not significant), and ARR was reduced by 77% (P < 0.001). Reduction of EDSS score and ARR did not depend on baseline ARR (1-2 vs >2) or EDSS score and was not biased by exceptional high disease activity or relapses around baseline. CONCLUSIONS: These real-life data reinforce that natalizumab is effective over years, reduces ARR, and stabilizes EDSS score independent of baseline ARR, baseline EDSS score, or baseline treatment.

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# Sustained efficacy of Natalizumab in the treatment of relapsing-remitting multiple sclerosis independent of disease activity and disability at baseline: real-life data from a Swiss cohort

Ulf Kallweit, MD; Ilijas Jelcic, MD; Nathalie Braun, MD, PhD; Heike Fischer, MD; Björn Zörner, MD; Bettina Schreiner, MD; Arseny A. Sokolov, MD; Roland Martin, MD; Michael Weller, MD; Michael Linnebank, MD

[1]*Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland*

Correspondence:

PD Dr. Michael Linnebank, Department of Neurology, University Hospital Zurich, Tel. +41 44 255 1111. Fax. +41 44 255 4380. Email: michael.linnebank@usz.ch

Running title: Natalizumab: Swiss real-life data

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**Abstract**

*Background:*

Therapy of relapsing-remitting multiple sclerosis with Natalizumab (Tysabri, Biogen Idec) has been shown to be effective in the reduction of the clinical relapse rate and disability progression. However, real-life, longitudinal data, including years before baseline, are rare.

*Methods*:

An observational, single-center study was carried out. We analyzed data from 64 consecutive MS patients.

*Results:*

After one year of treatment (n=64), EDSS decreased by 0.47 points (p=0.047), the annualized relapse rate (ARR) by 82% (p<0.001). After two years (n=41), EDSS was still reduced by 0.28 (n.s.) and ARR by 69% (p<0.001). After three years (n=23), EDSS was reduced by 0.26 (n.s.), ARR by 77% (p<0.001). EDSS and ARR reduction did not depend on baseline ARR (1-2 vs. >2) or EDSS and were not biased by exceptional high disease activity or relapses around baseline.

*Conclusion:*

These real life data reinforce that natalizumab is effective over years, reduces ARR and stabilizes EDSS independent of baseline ARR, baseline EDSS or baseline treatment.

**Kommentar [UK1]:** Ich finde, dass gehört nicht zwingend ins abstract

**Introduction**

In the pivotal trial of natalizumab therapy of relapsing-remitting multiple sclerosis (RRMS; AFFIRM) [1], the clinical relapse rate was reduced by 68% compared with placebo in the first year of treatment. Furthermore, the probability of disability progression was decreased [1]. Several subsequent studies have confirmed the efficacy of natalizumab [2-9]. However, real-life longitudinal data, including years before baseline and especially on patients with a high EDSS at baseline, are rare. The present study provides such real-life data on 64 natalizumab-treated MS patients with a mean baseline EDSS of 4.5±1.7.

**Patients and Methods**

We conducted our study in compliance with the principles of the Declaration of Helsinki. An observational, monocenter study was carried out. Inclusion criteria were natalizumab treatment of RRMS according to the modified McDonald criteria [10] and availability of standardized clinical data, collected in our MS center, on at least one year before and one year after initiation of natalizumab treatment. Relapses were defined according to McDonald criteria. PASW statistics version 18 was used for ANOVA statistics (IBM,NY). When data were only available for a subset of patients, e.g. the 2y and 3y follow-up data, we compared the available data with those patients' baseline data only and excluded baseline data of the other patients. Data were exploratively stratified by baseline EDSS, baseline ARR, median disease duration and prior therapies.

**Results**

Sixty-four consecutive patients were enrolled. Two additional patients developed persisting anti-natalizumab-antibodies, one developed an allergic reaction and one developed a progressive multifocal leukoencephalopathy (PML). These four patients were not included into further analyses. At baseline, mean age ±1 standard deviation was 41±10 yr. (range: 22-68). Forty-seven patients (0.73) were female, 17 (0.27) were male. Disease duration was 9.9±7.5 yr. (range: 0-29). Sixteen (0.25) patients had no prior immunomodulating or

immunosuppressive therapy other than steroids, 33 (52%) had been treated with beta-interferons only, 2 (3%) with glatiramer acetate only, 6 (9%) with both beta-interferons and glatiramer acetate one after another, and 7 (11%) had immunosuppressant treatment after beta-interferon and/ or glatiramer acetate treatment. Two patients had had an additional treatment with immunoglobulins.

Initiation of natalizumab treatment reduced the ARR in the entire population as well as in subgroups defined by a moderate or high ARR at baseline, respectively (*Table 1, Figure 1a*). The ARR was significantly reduced over the three years observed. In addition, natalizumab treatment also reduced the EDSS in the first year (*Table 1*). EDSS after two and three years was still lower in comparison to the baseline EDSS of the respective patients, but this was not significant, consistent with the smaller effect size and the smaller sample group. EDSS reduction was similar when stratified by limitation versus non-limitation of walking distance (*Figure 1b*). ARR and EDSS reduction were also independent of age, gender, or disease duration (not shown). Concerning patients without previous treatment, ARR baseline versus first year was 2.52±0.87 versus 0.38±0.74 (=85% reduction; p<0.001). For patients receiving therapy with interferons or glatiramer acetate before the time of natalizumab initiation, ARR baseline versus first year was 1.95±1.0 versus 0.29±0.46 (=85% reduction; p<0.001). In the first year of natalizumab treatment, EDSS improved in 22/64 (0.34) of patients and was stable in further 31/64 (0.48) patients. After two years, EDSS was better than baseline in 12/37 (0.32) and equal in 18/37 (0.49), and, after three years, EDSS was better in 6/23 (0.26) and equal in 13/23 (0.57). Clinical freedom of disease activity, i.e. no relapses and improved or stable EDSS, was observed in 43/59 (0.73), 13/37 (0.35), and 8/23 (0.35) patients after one, two and three years of natalizumab treatment. Regarding the years before baseline, ARR in the first year of treatment was significantly lower in comparison to one (p=0.012) and two (p=0.001) years before baseline, and also ARR of the second and third year after initiation was lower compared with one (p=0.017 and p=0.010) and two years (p=0.042 and

**Kommentar [UK2]:** Sollen wir hier noch dazu schreiben („data not shown“) Wenn wir noch eine Tabelle machen oder es in die Tabelle einfügen wird sie noch unübersichtlicher.
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p=0.022) before treatment initiation (*Table 1, Figure 1a*). This was not significant for EDSS (*Table 1*).

**Discussion**

Natalizumab has been shown to be effective in the treatment of RRMS [1-9]. However, longitudinal real-life data are rare. The Swedish national post-marketing surveillance study demonstrated sustained efficacy of natalizumab treatment for the Swedish population [9]. For the present population, similar results were obtained with data collected in our MS-center standardized to the McDonald criteria [10].

Natalizumab treatment is often initiated after a period of active disease resulting in a high baseline ARR. It cannot be excluded that, in the natural course of disease, the ARR of the next year would have been lower again, even without initiation of natalizumab therapy. Natural regression to the mean disease activity might be an important bias in respective studies using baseline data for the analysis of natalizumab efficacy, as Natalizumab often is initiated in a periods of high disease activity. Thus, comparison of follow-up data during Natalizumab therapy should not only been performed with baseline, but also with the disease activity before baseline. In our study, the ARR in the first three years was significantly lower not only in comparison to baseline data, but also to one and two years before baseline, demonstrating a sustained efficacy not derived from a bias concerning the evaluation of baseline data. Moreover, ARR reduction in the first year was identical in patients without treatment and patients under treatment with interferons or glatiramer acetate at treatment initiation. These data confirm the efficacy of natalizumab in patients with active disease, regardless if treatment naïve/ currently untreated or under first-line immunomodulating therapy. In our group of patients, the efficacy of natalizumab over three years according to the reduction on ARR and, in part, EDSS, was confirmed. The effect of natalizumab on patients with more advanced disease severity, i.e. with a reduced walking distance, was comparable to patients without reduced walking distance showing a remarkable stabilization

**Kommentar [ML3]:** immer gross oder klein

and slight improvement on EDSS indicating the positive effect of Tysabri on EDSS compared to the natural course of the disease. [11]

**Conclusion**

In conclusion, our study reinforces that natalizumab is efficient in the treatment of RRMS independent of baseline ARR, baseline EDSS or baseline treatment. Improvement after baseline is not likely to be biased by exceptionally high disease activity at the time-point of Tysabri initiation as shown by the data from year(s) before baseline. Efficacy of natalizumab therapy persists over years. The benefits of natalizumab treatment must be weighed against the risks.

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**Kommentar [ML4]:** im text nur bis ref 11, ist da was verschoben?

**Figure title and legend:**

Figure 1a: Annualized replapse rate

Annualized relapse rate (ARR) before and after initiation of natalizumab treatment. * p<0.05, ***p<0.001

Figure 1b: EDSS

EDSS differences from baseline (t=0: EDSS=4.52) beginning two years before to three years after therapy. * p<0.05, **p<0.01

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